6 A. Guarnieri, G. Scapini, S. Burnelli, I. Busacchi und L. Varoli, Farmaco Ed. Sci. *34*, 704 (1979).
7 P. F. Jubi in Antiinflammatory Agents, R. A. Scherrer and M. W.Whitehouse Eds., Vol. 1, p. 91, Academic Press, New York 1974.
8 Houben-Weyl, Methoden der organischen Chemie, Band 4/2, Thieme Verlag, Stuttgart 1955.
9 C. A. Winter, E. A. Risley und G. W. Nuss, Proc. Soc. Exp. Biol. Med., *11*, 544 (1962).

[Ph 336]

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Studies on Coumarins, I

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4-Bromomethylcoumarins, prepared by the reaction of phenols and 4-bromoethyl acetoacetate, were reacted with primary aromatic amines to yield 4-anilinomethylcoumarins. The spectral properties and antimicrobial activities against five micro-organisms are reported.

Untersuchungen über Cumarine, 1. Mitt.

4-Brommethylcumarine, hergestellt durch Umsetzung von Phenolen mit 4-Bromethylessigester, werden mit primären Aminen umgesetzt, um 4-Anilinomethylcumarine zu erhalten. Über ihre spektralen Eigenschaften und über ihre antimikrobielle Aktivität gegen fünf Mikroorganismen wird berichtet.

The coumarin nucleus is the seat of diverse biological activities through innumerable derivatives[1]. A number of 4-methyl and 4-aminomethyl derivatives of coumarin are known to exhibit powerful CNS stimulating[2] and vasodilatory[3] activities. Broad spectrum antibiotic activity of many naturally occurring coumarins has been interpreted[4] as due to -O-C=C-$(C)_n$-O- structural moiety where n = 2, 3 etc. Recently *Shridhar* et al.[5] synthesised many 4-[2-(heteroaryl)vinyl]coumarins as potential anti-microbial agents against K. pneumoniae and M. tuberculosis. The anilino group is known for its vital role in many antimalarials[6], anti-mycobacterial agents[7], and B. subtilis inhibitors[8]. In the light of the above observations it was thought of interest to combine the coumarin ring and the anilino groups with a view to study the biological properties of the resulting compounds.

The present investigation reports the synthesis of a series of 4-anilinomethylcoumarins and their spectral properties. These compounds have been screened for antibacterial activity against five micro-organisms.

The required 4-bromomethylcoumarins **1** were prepared according to literature methods[9,10]. The reaction of these with various aromatic primary amines was carried out at

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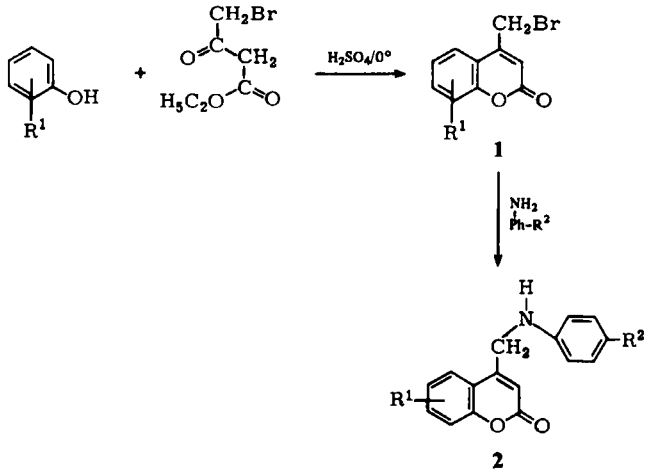
elevated temperatures employing large excess of the amine. The 6-chloro- and 7-chloro-4-bromomethylcoumarins were prepared from p-chlorophenol and m-chlorophenol respectively[11]. The reactions are presented under scheme-A.

Scheme – A



In the infrared spectra (KBr), compounds **2** exhibited strong bands around 3400 cm^{-1} and 1700 cm^{-1} due to -N-H and C=O stretching vibrations[12]. In the region of 1500–1600 cm^{-1} three bands of medium intensity, characteristic of skeletal aromatic C=C stretching modes were found. A strong band around 1600 cm^{-1} (except for R^2 = H) was observed due to the p-disubstituted benzene ring[13]. The C=C stretching of the 3,4-double bond appeared around 1620 cm^{-1}. Three to four bands of medium intensity were found in the region of 1100–1300 cm^{-1} due to the C-O-C stretching vibrations[13]. Infrared spectral data for some of the compounds are presented in table 2.

The NMR spectra of compounds **2** have been examined in deuterochloroform and trifluoroacetic acid solutions. In the compound **b**, of the two methyl groups the 6-CH_3, resonates downfield at 2.46 ppm while the -CH_3 group in the aniline moiety appears at 2.30 ppm. The exchangable N-H proton appears as a broad hump around 4.1 ppm. In trifluoracetic acid solution, due to the protonation of the nitrogen lone pair, the $N^{\oplus}$-H proton is shifted downfield and gets buried among the aromatic protons[14]. The methylene protons which no longer experience the shielding effect of the nitrogen lone pair in TFA, resonate at 5.03 ppm compared to 4.50 ppm in $CDCl_3$ solution. Similar effect can be observed with the 3-proton as well. The aromatic protons appear around 7.0 ppm. The NMR spectral data are shown in table 3.

Among all the compounds tested for their antibacterial activity against E. coli, S. aureus, P. vulgaris, B. subtilis and A. aerogenes by the agar plate technique, it is observed that the compounds **2c, p, l** and **t** showed complete inhibition of the growth of E. coli but were less active against other strains, and the rest were inactive.

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Table 1: *Compounds* **2**

2	R^1	R^2	m.p. °C	Yield %	Formula*	Calc. N	Found N
a	6-CH_3	-H	195-196[a]	70	$C_{17}H_{15}NO_2$	5.3	5.2
b	6-CH_3	-CH_3	183-184[a]	80	$C_{18}H_{17}NO_2$	5.0	4.8
c	6-CH_3	-Cl	212[a]	89	$C_{17}H_{14}NO_2Cl$	4.6	4.4
d	6-CH_3	-OCH_3	234-235[a]	84	$C_{18}H_{17}NO_3$	4.7	4.4
e	7-CH_3	-H	137-138[a]	84	$C_{17}H_{15}NO_2$	5.3	5.1
f	7-CH_3	-CH_3	159-160[a]	85	$C_{18}H_{17}NO_2$	5.0	5.3
g	7-CH_3	-OCH_3	124-125[a]	87	$C_{18}H_{17}NO_3$	4.7	4.5
h	7-CH_3	-Cl	170-171[a]	90	$C_{17}H_{14}NO_2Cl$	4.6	4.8
i	7-MeO	-H	162-163[b]	85	$C_{17}H_{15}NO_3$	4.9	4.7
j	7-MeO	-CH_3	159-160[a]	82	$C_{18}H_{17}NO_3$	4.7	4.5
k	7-MeO	-OCH_3	172-173[a]	88	$C_{18}H_{17}NO_4$	4.5	4.4
l	7-MeO	-Cl	174-175[a]	86	$C_{17}H_{14}NO_3Cl$	4.4	4.3
m	6-Cl	-H	100-101[a]	80	$C_{16}H_{12}NO_2Cl$	4.9	5.1
n	6-Cl	-CH_3	198-199[a]	87	$C_{17}H_{14}NO_2Cl$	4.6	4.3
o	6-Cl	-OCH_3	185-186[b]	84	$C_{17}H_{14}NO_3Cl$	4.4	4.2
p	6-Cl	-Cl	232-233[d]	82	$C_{16}H_{11}NO_2Cl_2$	4.3	4.1
q	7-Cl	-H	102-103[a]	79	$C_{16}H_{12}NO_2Cl$	4.9	4.7
r	7-Cl	-CH_3	189[c]	78	$C_{17}H_{14}NO_2Cl$	4.6	4.8
s	7-Cl	-OCH_3	172-173[b]	80	$C_{17}H_{14}NO_3Cl$	4.4	4.5
t	7-Cl	-Cl	176[b]	82	$C_{16}H_{11}NO_2Cl_2$	4.3	4.5

Crystallisation from: a = aqueous ethanol or ethanol; b = benzene; c = ethylacetate; d = mixture of dioxan, ethanol and water. * All the compounds gave satisfactory C, H analyses.

Table 2: *IR spectra (KBr)*

2	N-H (cm^{-1})	C=O (cm^{-1})	2	N-H (cm^{-1})	C=O (cm^{-1})
a	3400	1720	i	3385	1705
b	3390	1720	n	3380	1705
c	3380	1710	p	3385	1710
e	3420	1720	s	3390	1705

Table 3: *NMR spectra*

2	Solvent	3-H	4-CH_2-N	Ar-H	N-H	R^1	R^2
b	$CDCl_3$	6.58	4.50	6.9-7.4	4.1	2.46	2.30
b	TFA	6.76	5.03	7.3-7.6	7.7	6 H	2.44
g	TFA	6.73	5.13	7.1-7.6	7.75	2.46	4.06

Experimental

MP: open capillaries (uncorr.). *IR spectra*: Carl-Zeiss UR-10. *NMR spectra*: Varian A-60. Chemical shift: (δ) ppm downfield from TMS.

4-Anilinomethylcoumarins **2**, *General method*

In a dry round bottom flask 4.0 mmole of the 4-bromomethylcoumarin and 40.0 mmole of an arylamine were mixed and heated over free flame for a few min to obtain a solution. The flask was cooled to room temp. and 5 ml glacial acetic acid were added. The solution was then heated in an oil-bath between 120–130° for 1 h. The cooled product was stirred with 200 ml 5 % hydrochloric acid. The separated solid was washed with water and recrystallised (table 1).

Anti-microbial studies

The test compounds were dissolved in purified DMF at a concentration of 2000 μg/ml. Each agar plate was treated with 0.1 ml of the test solution and the zone of inhibition was measured after 24 h. Phenol was employed as standard.

References

1 G. Feuer in Progress in Medicinal Chemistry, p. 86, ed. G.P. Ellis and G.B. West, North-Holland Publishing Comp., New York 1974.
2 V. N. Gupta, B. R. Sharma and R. B. Arora, J. Sci. Ind. Res. *20B*, 300 (1961).
3 Laboratories Dausse, S.A. Fr, M. 2035, C.A. *60*, 4114a (1964).
4 Ref. 1, p. 116.
5 D.R. Shridhar, C.V.R. Sastry, N.K. Vaidya, S.R. Moorthy, G.B. Reddy, G.S. Thapar and S.K. Gupta, Indian J. Chem. *16B*, 704 (1978).
6 R. M. Pinder in Medicinal Chemistry, Vol. I, p. 498, A. Burger Ed.,Wiley-Interscience Publishing Comp., New York 1970.
7 A. Lewis and R.G. Shepherd, ibid. p. 444.
8 G.E. Wright and N.C. Brown, J. Med. Chem. *23*, 34 (1980).
9 Y. S. Agasimundin and S. Siddappa, J. Karnatak Univ. *15*, 1 (1970).
10 B. B. Dey and Y. Shankaranarayanan, J. Indian Chem. Soc. *11*, 687 (1974).
11 Ph. D. Thesis, *M. V. Kulkarni*, Karnatak University 1980.
12 P. Basignana and C. Cogrossi, Tetrahedron *20*, 2859 (1964).
13 L.J. Bellamy, The Infrared Spectra of Complex Molecules, Vol. I, p. 72, p. 129, Chapman and Hall, London 1975.
14 W.R. Anderson, Jr. and R.M. Silverstein, Anal. Chem. *37*, 1417 (1965).
15 A. Burger and G.E. Ullyot, J. Org. Chem. *12*, 346 (1947).

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